REMARKS

I. Status of the Claims

Claims 2-5, 7-10, 19-58 and 62-64 are pending in the application. Claims 1, 6, 11-18, 59 and 60 have been canceled and claims 2-5, 7-10 and 20-58 have been withdrawn pursuant to an election of species. Claims 19 and 62-64 have been examined and are rejected under 35 USC §112, first paragraph, 35 USC §112, second paragraph, 35 USC §102 and 35 USC §103.

II. Rejection Under §112, First Paragraph

Claim 19 remains rejected under §112, first paragraph on the grounds that the specification does not provide any evidence that administration of UTAA will "enhance" the production of antibodies and, further, that there is no demonstration of prevention or treatment of cancer following administration of UTAA. Applicants respectfully traverse the rejection. In order to delineate the issues more clearly, applicants have separated out the "enhancing" and "inducing" aspects of claim 19. New claim 65, which recites enhancing antibody production, is believed to be the only claim subject to this rejection. Therefore, the following comments are provided in support of new claim 65.

In the last response, applicants argued that both the composition claims and methods of use therefore were sufficiently supported by the diagnostic aspect of the application, namely, that UTAA could be used to immunize subjects to produce antibodies which, in turn, could be used to diagnose cancer. This premise has not been challenged and, in fact, the rejection as it applied

to composition claims 62-64 has been withdrawn. Thus, it appears to be the examiner's position that a claim to "enhancing" antibody production may only be supported by a therapeutic utility.

The examiner has failed to advance any scientific reasoning against the operability of the claim 65 with respect to either diagnostic or therapeutic utility. Thus, on its face, the rejection is fatally flawed. It is well established law that the first paragraph of §112 requires nothing more than objective enablement. *In re Marzocchi*, 169 USPQ 367 (CCPA 1971). To bring the objective enablement of the claims into question, it is incumbent upon the examiner to come forth with some evidence supporting the alleged non-enablement of rejected claims. *In re Dinh-Nguyen*, 181 USPQ 46 (CCPA 1974).

The only "reasoning" given in support of the rejection is the lack of examples. Yet examples are not required to establish sufficient support for claims under §112 so long as the invention may be practiced without undue experimentation. *In re Borkowski*, 164 USPQ 642 (CCPA 1970). It is the examiner's burden to show that the disclosure necessitates undue experimentation. *In re Angstadt*, 190 USPQ 214 (CCPA 1976). Here, where no such showing has been made, the rejection should not be sustained.

In fact, the specification contains more than enough disclosure regarding enhancement of antibody production to support new claim 65. As described in the Background, many melanoma patients have antibodies against UTAA. Page 7, lines 25-33. In such patients, further administration of purified UTAA would be expected to stimulate the production of

antibodies, and the examiner has offered no reason why this would not be the case. In the attached declaration of Dr. Gupta, the antibody titers of four melanoma patients are shown following administration of UTAA. In each case, the anti-UTAA titers rose significantly following administration.

And while the serum of human cancer patients may not be the most common source for antibodies, it certainly can be used for such. In fact, the antibodies produced by cancer patients might well be distinct in reactivity from those produced in subjects that are not afflicted. Therefore, enhancing antibody production may constitute another diagnostic aspect of the present invention. Applicants respectfully request reconsideration and withdrawal of the rejection.

III. Rejection Under 35 USC §112, Second Paragraph

Claim 19 stands rejected under §112, second paragraph as allegedly indefinite. According to the examiner, the terms "induce" and "enhance" in the preamble of claim 19 are not equivalent and, therefore, the claim is vague and confusing. Applicants respectfully traverse the rejection.

The alternative terminology "or" is not *per se* impermissible claim language. Rather, such claims must be interpreted for definiteness as any other claim. In the instant circumstance, applicants agree with the examiner that induction of antibody production and enhancement of antibody production are completely different things. Webster's Collegiate Dictionary, 10th Ed.

(1993) defines "induce" as "to cause the formation of" and "enhance" as "to increase or improve in value." Neither of these terms are vague or indefinite.

In the context of the present claim, the application of either term to antibody production is perfectly clear. In the situation where no prior antibody production has occurred, the administration of UTAA results in the induction of antibodies to this antigen. In the case where antibodies previously have been produced or are being produced, the administration of UTAA results in the enhancement of antibody production. These concepts are clear to those of skill in the art and, in the absence of a further explanation of why the claim is indefinite, applicants submit that the rejection is improper.

In the interest of advancing the prosecution, however, applicants have separated the "inducing" and "enhancing" aspects of claim 19, which now refers only the former function, and have provided new claim 65 drawn only to the latter. Applicants respectfully request reconsideration and withdrawal of the rejection.

IV. Rejection over Real

Claims 19 and 62 are rejected under §102(b) as allegedly anticipated by Real *et al.* (U.S. Patent 4,562,160). Real is said to disclose an antigen composition comprised of a tumor associated antigen having a molecular weight of 90-100 kD which is useful for antibody production. Presumably, the examiner maintains that UTAA may be Real's antigen, designated

"FD," and in the absence of evidence that UTAA and FD are not the same, the rejection stands.

Applicants again respectfully traverse the rejection.

It first will be useful to review briefly the previous response:

> First, the examiner is quite correct in noting that UTAA, under reducing conditions, runs at about 90-100 kD in PAGE. Nonetheless, it also is true that UTAA holoantigen runs at 590-620 kD under non-reducing conditions. Given these figures, what can be said regarding the molecular weight of Real's FD? As the examiner likely has observed, Real notes that FD runs at 90 kD on PAGE (column 4, line 59; column 5, line 8). It is important to note that at column 3, lines 12-15, Real describes the treatment of "unreduced samples." The only reasonable inference one can draw, reading the reference as a whole, is (i) that both reducing and non-reducing gels were run and (ii) that under either analysis, FD ran at 90 kD.
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> Turning to the question of prevalence on melanoma cells lines, applicants concede the veracity of the examiner's abstract statement that one cannot rely on limitations not recited in the claims to distinguish over the prior art. That, however, is not the situation at hand. Claim 62 recites "Urinary Tumor Associated Antigen (UTAA)." This term is defined by the specification, for example, at pages 32-33, where it is reported that sera from 63% of disease-bearing melanoma patients showed reactivity with UTAA. In another test for anti-UTAA activity, described at pages 58-60, it was shown that some 37% of patients had sera which recognized UTAA. It now has been confirmed that 70-75% of melanoma cell lines express UTAA. When compared with the prevalence of FD on melanoma cells (<3%), it is clear that UTAA, as defined in the specification, is not the same as FD.
>
> Taken separately, the showing regarding the difference in molecular or the difference in prevalence on melanoma cells would be sufficient to rebut the examiner's allegation of anticipation. Taken together, there should be no question that the present invention is distinguishable from that disclosed by Real.

The examiner has responded by arguing that (i) the Real reference discloses both reducing and non-reducing conditions and that it is unclear what the molecular weight of Real's starting

material is and (ii) that it is unclear how applicants have determined that Real's antigen is found on less than 3% of melanoma cells.

In response, applicants point out again that Real's discussion of reducing and non-reducing conditions in the absence of any mention of higher molecular weights, indicates that no high molecular weight form of Real's antigen was observed. In the absence of a high molecular weight species, the only logical conclusion is that Real's antigen the UTAA subunit claimed here, are distinct.

The examiner's assertion that Real did not look at tissue distribution is not correct. Real describes absorption analysis of immune serum with multiple types of cancer cells, both melanoma and non-melanoma. Column 4, lines 9-25. It is stated that only one melanoma line out of 34 tested was found to express the Real antigen, and that particular cell line was comprised of autologous cells of the very same patient from whom the serum (antibody source) was obtained. Hence, less than 3% of those individual melanoma cells tested by Real were found to express FD. This stands in marked contrast to similar studies with UTAA, which is known to be expressed in multiple types of cancer, including 70% of melanomas. Again, the only plausible conclusion is that the two antigens are distinct.

There is no available anti-FD antibody, so no side-by-side comparison of FD antigen and UTAA 90-100 kD subunit is possible. Applicants submit, however, that the following tables comparing clearly demonstrate that FD and UTAA are distinct:

TABLE 1: CHARACTERISTICS OF UTAA AND FD ANTIGEN

Characteristic or property	90-kD subunit of urinary tumor-associated antigen	90-kD (Class I) Melanoma tumor antigen
Discovered by	Morton *et al.*	Real *et al.* (U.S. Patent Number 4,562,160)
Defined using	Allogeneic serum samples	Autologous serum
Reacts with:		
murine monoclonal	AD1-40F4	Not reported
allogeneic Ab's	Yes	Not reported
xeno-antibody	Baboon	Not reported
Epitope	Protein	Not reported
Isoelectric point	6.1	5.5
Sialic acid	Not detectable	Antigenic activity not affected by its removal
Antigen activity affected by mixed glycosidases	No	Not reported
Binds with lectin	Wheat germ agglutinin	Concanavalin—A
Heat stable	Yes (100°C for 5 min.)	No (100°C for 5 min.)
Can be detected in:		
serum	Yes	Not reported
urine	Yes	Not reported
Expressed by:		
melanomas	Yes (most — 71%)	Yes (very few)
sarcomas	Yes (most — 67%)	No
neuroblastoma	Yes (most — 75%)	No
carcinomas:		
breast	Yes	No
colon	Yes	No
lung	Yes (most — 80%)	No
prostate	Yes	No
ovary	Yes	No

In light of the foregoing remarks and evidence, applicants respectfully submit that the rejection is improper and request that it be withdrawn.

V. Rejection Over Euhus

Claims 19, 62-64 are rejected as anticipated or rendered obvious by Euhus *et al.* According to the examiner, Euhus discloses a 110 kD version of UTAA that appears to be the same antigen as that claimed, or at least an obvious variation thereof. In addition, Euhus is said to disclose the production of antibodies, implying the administration of the antigen to an animal for the purpose of eliciting UTAA-reactive antibodies. Applicants respectfully traverse the rejection.

First, it should be noted that each of the claims now recites a substantially purified form of the 90-100 kD subunit of UTAA. See specification at page 15, line 2 and Example I for support. The Euhus abstract, in contrast, provides only a crudely purified form of UTAA derived from serum. Thus, on its face, the Euhus abstract does not meet the limitations of the claims as amended herein.

Second, It is well established that a reference must teach how to make and use, *i.e.*, must enable the claimed invention for it to be a valid against the claims of an application. In *Paperless Accounting Inc. v. Bay Area Rapid Transit Sys.*, 231 USPQ 649 (Fed. Cir. 1986), the PTO's reviewing court said that a "§102(b) reference 'must sufficiently describe the claimed invention to have placed the public in possession of it'.... '[E]ven if the claimed invention is

disclosed in a printed publication, that disclosure will not suffice as prior art if it was not enabling.'"

Thus, even if a substantially purified UTAA subunit was described in the Euhus abstract, which applicants deny, the reference contains insufficient enabling disclosure for the purification thereof. The methodology necessary to successfully isolate UTAA from serum is not adequately described in the Euhus abstract, however. Isolation of a new molecule from a complex sample such as serum requires considerable empirical study to determine what conditions, if any, will permit purification. No such studies are disclosed in the abstract. The absence of such parameters from the abstract would have precluded those of skill in the art from reproducing the work of the inventors without undue experimentation. Thus, the independent claims can be neither anticipated or rendered obvious by the abstract.

Third, the abstract also clearly does not describe UTAA purified 100+-fold and purified to at least 0.6% of total protein, as recited in dependent claims 63 and 64, respectively. Moreover, these claims could not be obvious over Euhus given that there is no suggestion of how to achieve these levels of purity, as stated above.

For all of the foregoing reasons, applicants submit that the Euhus abstract is insufficient to teach or suggest the present invention. Rather, it merely describes a preliminary stage in research that eventually developed into the present invention. Because the abstract is deficient both in a description of the claimed invention and in enabling technology that would permit

reproduction thereof, rejections based thereon are improper. Reconsideration is respectfully requested.

VI. Rejection Over Paulie

Claims 62-64 are rejected as anticipated or rendered obvious by Paulie *et al.* According to the examiner, Paulie discloses a 92 kD antigen associated with bladder carcinoma that appears to be same antigen as that claimed, or at least an obvious variation thereof. Applicants respectfully traverse the rejection.

Attached hereto is a declaration from one of the inventors, Dr. Rishab Gupta. Dr. Gupta obtained samples of anti-92 kD monoclonal antibodies from Dr. Staffan Paulie, the lead author of the Paulie paper. As can be seen from the Western blots attached to the declaration, the UTAA subunit-reactive antibody identified as C6 binds to a 90-100 kD band from a purified extract of UTAA. Neither antibody provided to Dr. Gupta by Dr. Paulie, previously shown to bind to the 92 kD antigen of the reference, binds to this band. Thus, it is clear that the antigen identified by Dr. Paulie, using antibodies 7E9 and P7A5, is immunologically unrelated to 90-100 kD subunit of UTAA. Thus, applicants submit that the record does not support the examiner's inference that the Paulie antigen and that claimed here are the same.

Turning to the obviousness, rejection, there is nothing in the Paulie reference to suggest the existence of a melanoma antigen distinct from the identified 92 kD carcinoma antigen. Any

comparison of the Paulie antigen with UTAA is pure hindsight and cannot be supported. Applicants therefore respectfully request reconsideration and withdrawal of both rejections.

VII. Summary

In light of the foregoing amendments and remarks, applicants submit that all claims are in condition for allowance and solicit an early indication to that effect. Should Examiner Sidberry feel that further discussion of any remaining issues would advance the prosecution, she is invited to contact the undersigned at the telephone number listed below.

Respectfully submitted,

STEVEN L. HIGHLANDER
Reg. No. 37,642

9/18/95
Date

FOL
David L. Parker
Reg. No. 32,165

Attorney for Applicants

ARNOLD, WHITE & DURKEE
P. O. Box 4433
Houston, TX 77210
(512) 418-3000

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